REMARKS

Withdrawal of Finality of Official Action

On July 25, 2001, Applicants filed a Request for Withdrawal of Finality of the Office Action of May 9, 2001. The Examiner has indicated that the finality will be withdrawn upon filing of a response to the official action (interview summary record mailed September 4, 2001).

The Claimed Invention:

The claimed invention is directed to a method for screening for drugs for the treatment of Alzheimer's disease, and to slices of mouse hippocampal tissue containing cells having a mutation in a presenilin gene combined with a candidate drug upon filing of this response.

The Pending Claims:

Prior to entry of the above amendments, Claims 1 and 3-13 are pending. Claims 1-5, 7-9 and 13 are directed to a method for screening for drugs for the treatment of Alzheimer's disease. Claim 6 is directed to a method for determining whether a mutation in hippocampal cells acts on a common pathway with a $GABA_A$ receptor antagonist. Claims 10-12 are directed to slices of mouse hippocampal tissue.

The Office Action:

Claims 1 and 3-13 are rejected under 35 U.S.C. § 112, first paragraph, enablement.

Claims 6 and 8-9 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite to use of the phrase "significant change."

The information disclosure statement filed 2-16-01 fails to comply with 37 CFR(a)(2) which requires a legible copy of each US and foreign patent.

Claims 1 and 3-13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of US patent No. 09/193,221.

Claims 10-12 are rejected under 35 U.S.C. § 112, first paragraph, written description (new matter).

Claims 1 and 3-13 are rejected under U.S.C. § 112, first paragraph, written description

(syntax error).

Claims 1 and 3-13 are rejected under U.S.C. § 112, first paragraph, written description (use of the phrase "presenilin gene mutation").

Amendments:

Claims 1, 5, 6, 8 and 9 have been amended by changing the phrase "contacting mutant hippocampal cells, with a presenilin gene mutation" to --contacting hippocampal cells comprising a presenilin gene mutation--. Support for the amendment to correct this syntactic error is provided by Claims 1, 5, 6, 8 and 9 as filed.

New Claims 14-26 have been added. Support for new claims 14-21 may be found in Claims 2-11 as filed, and on page 2, lines 3-4; page 5, lines 12-14; page 6, lines 16-19; and page 7, line 1. Support for new Claims 22-25 may be found in Claims 10-12 as filed and on page 9, lines 18-29. Support for new Claim 26 may be found on page 9, lines 18-29.

No new matter has been added by the amendments and the Examiner is requested to enter them.

Response to Rejections:

In the response that follows, the Examiner's specific objections and rejections are reiterated in small bold indented print, followed by Applicants' response, which is identified by normal print.

35 U.S.C. 112, first paragraph

Applicants arguments filed 2-16-01 have been fully considered but are not persuasive. With respect to applicants argument that the cells are required to have enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells and thus do not possess unreliable or unpredictable effects, the examiner notes that the applicants exemplification of such cells is limited to a single mutation effect. As previously noted the art of predicting protein function based upon variant structure is unpredictable, see in particular Skolnick et al., Trends in Biotech., 18(1):34-39, 2000. Further with respect to applicants claims the specification fails to teach a scope of presenilin mutations which exhibit enhanced synaptic potentiation upon tetanic stimulation in comparison to wild-type cells. Thus the scope of the claims is not commensurate with the scope of enablement. With respect to Parent et al., it is noted that applicants point to support for enablement of applicants claims as Parent teaches (as supported in the Parent et al., abstract) that following "theta burst stimulation or high frequency stimulation, input-specific LTP in Mtg (mutant transgene) animal had a larger initial amplitude and was more persistent than in WtTg or Ntg (wild-type or non-transgenic)

animals. However, it is als noted in the Parent et al., abstract, Figure 1 and Table 1 that basal synaptic transmission was unaltered in Mtg, WtTg or Ntg mice including maximum fiber volley amplitude, fEPSP amplitude, slope, and paired-pulse facilitation (a form of repeated/tetanic stimulus). Thus, the effects do not appear to be correlated with enhanced synaptic potential following general tetanic (repeated) stimuli since paired pulse facilitation was no different among groups. Instead it appears that the fEPSP differences observed in mutant presenilin cells occurs only following stimuli which induce long term potentiation, which elements are not specifically claimed. Applicants are further directed to the teaching of Kandel et al., Principles of Neural Science, Elsevier, 3rd Ed., 1991, pp. 206-209, and 1019-23, in particular to the requirements and description of long term potentiation.

In order to satisfy the enablement rejection of section 112, a patent application must contain a description that enables one skilled in the art to make and use the claimed invention. Atlas Powder Co. v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). When a patent specification contains a teaching of a manner and process of making and using the invention in terms that correspond in scope to those used in defining the claimed subject matter, it is presumptively enabling, whether it sets forth that teaching "by the use of illustrative examples *or by broad terminology*." (emphasis added) *In re Marzocchi* 169 USPQ 367, 369 (C.C.P.A. 1971). To overcome that presumption, the Examiner must set forth reasons to doubt the objective truth of the statements contained therein; i.e., the Examiner must explain why the accuracy of a statement is doubted and support that explanation with acceptable evidence. The Examiner has erred in that she did not provide acceptable evidence for finding that the claims are not supported by an enabling disclosure. The Examiner has simply not provided acceptable evidence for doubting Applicants' teaching that the claimed methodology can be used for cells or tissues with enhanced synaptic potentiation.

With regard to the Examiner's statement that "applicants exemplification of such cells is limited to a single mutation effect", Applicants respectfully point out that the present claims are directed to methods for using cells or tissues which have a desired effect (enhanced synaptic potentiation upon stimulation" after "tetanic stimulation") rather than to the presenilin mutation itself. Cells or tissue comprising the presenilin mutation which produces the effect of enhanced synaptic potentiation will suffice, and the claims are enabled by the numerous examples in the specification that support the observed effect. Applicants also point out that "the art of predicting protein function based upon variant structure is unpredictable" is not an issue here, but

rather the art of observing cell or tissue response after tetanic stimulus is. Since, as stipulated by the claims, the cells or tissue ***must*** have enhanced synaptic potentiation upon stimulation, it stands to reason that the same cells or tissue will ***enable*** one to observe the claimed reduction in the enhanced synaptic potentiation if and when it occurs. This requirement for a stipulated cellular behavior is, by definition, predictable in the present context. By her statement, the Examiner is suggesting that there may be one or more presenilin gene mutations associated with cells or tissues that have enhanced synaptic potentiation, and that somehow interfere with or obscure the reduction in the enhanced synaptic potentiation. The Examiner has not provided any reasons or justification for how this may occur other than the statement that mutations produce unpredictable results. Applicants point out that electrophysiology is a well-known and long-used art, that enhanced synaptic potentiation would be recognized by the skilled artisan, and that cells that possess this characteristic may be readily and successfully used by the skilled artisan without undue experimentation.

With regard to the Examiner's statement that "basal synaptic transmission was unaltered in Mtg, WtTg or Ntg mice including maximum fiber volley amplitude, fEPSP amplitude, slope, and paired-pulse facilitation (a form of repeated/tetanic stimulus)", Applicants respectfully point out that *facilitation* is a more transient form of synaptic plasticity that *potentiation*. In *facilitation*, growth of postsynaptic potential increases and decays rapidly, each generally within a second or less. However, the claims are directed to synaptic *potentiation*, a gradual rise in postsynaptic potential occurring over 1 second to tens of seconds followed by a ***slow*** decay (see Zucker, (1989); page 13;, Winder *et al.*, (1998)) pages 27-28). Thus, the Parent observations based on paired pulse facilitation are irrelevant to the presently claimed invention.

With respect to applicants arguments concerning the enablement of the screening method to identify candidate drugs for the treatment of Alzheimer's Disease, the Examiner understands applicants suggestion to be that the administration of drugs identified as capable of reducing synaptic potentiation (LTP) in mutant hippocampal cells is probable and desirable to treat Alzheimer's. However, in contrast to this suggestion the art recognizes that a drug which reduces synaptic potentiation (a model of learning and memory) would be counterintuitive to treating Alzheimer's. Instead it would appear that such a drug would likely lead to an exacerbation of the learning and memory deficits associated with the disease. There is no evidence that the enhanced fEPSP slope in the presenilin mutant cells contributes to Alzheimer's or is aberrant as applicants suggest. Further, there is no recognition that blockade of synaptic potentiation is beneficial for screening drugs for the treatment of Alzheimer's Disease. An alternative suggestion could be that the observation is a mere

epiphenomena or a compensation response resulting from the predisp sing effects of the presenilin mutation.

With regard to this part of the rejection, particularly "There is no evidence that the enhanced fEPSP slope in the presenilin mutant cells contributes to Alzheimer's or is aberrant as applicants suggest," and "there is no recognition that blockade of synaptic potentiation is beneficial for screening drugs for the treatment of Alzheimer's Disease". Applicants respectfully point out that this appears to be a utility rejection than an enablement rejection. Applicants have taught how to make and use the invention throughout the specification, and thoroughly represented the invention with numerous examples.

Applicants do *not* suggest that administration of drugs capable of reducing LTP in mutant hippocampal cells is probable and desirable to treat Alzheimer's. The present invention is directed to screening methods, not to treatment.

With respect to the Examiner's assertion that "the art recognizes that a drug which reduces synaptic potentiation (a model of learning and memory) would be counterintuitive to treating Alzheimer's", Applicants note that the pre-filing reference of Fastbom (cited in the IDS filed February 6, 2001) and the post-filing reference of Zaman *et al.* ((2000) *Neurobiol Disease* 7: 54-63; see discussion below) confirm the operability of the present invention, including, for example, with drugs that act as $GABA_A$ potentiating agents such as benzodiazepines, as noted below.

It is well known in the art that LTP is triggered by NMDA receptor channels opening during depolarization of postsynaptic neurons from their normal resting levels. Depolarization expels Mg^{+2} from the NMDA channel, which allows current to flow into post-synaptic cells. Since the NMDA channel is permeable to Ca^{+2}, the result is a significant influx of Ca^{+2} into the cell, which in turn triggers LTP. Ca^{+2} homeostasis is thus disrupted. It is well known in the art that, over time, altered Ca^{+2} homeostasis may lead to neuronal damage (see reference to Zaman, which, as previously noted, states that constant increase in intracellular calcium during neuronal stimulation may cause hippocampal neurons to die or function improperly).

Zaman *et al.* found enhanced LTP in presenilin-1 mutant expressing brain slices at CA1

pyramidal neurons. In addition, they proposed that the increase in synaptic plasticity due to enhanced calcium release may alter $GABA_A$ inhibitory input at the CA1 hippocampal neuron. Zaman used pharmacologic manipulation to either inhibit or enhance $GABA_A$ inhibitory transmission. Normally, in non-transgenic mice brain slices, when $GABA_A$ is inhibited by picrotoxin, LTP is enhanced and when $GABA_A$ is potentiated with a benzodiazepine, LTP is decreased. However in Zaman's PS1 mutant transgenic mice brain slices, $GABA_A$ inhibition produced no effect and $GABA_A$ potentiation restored LTP to wild-type controls. This finding suggested that $GABA_A$ inhibition was upregulated in PS1 mutant expressing mice to compensate for the enhanced synaptic excitatory activity.

On the simplest level one might speculate that alterations in LTP, either increased or decreased, could lead to alterations of learning and memory that are associated with the progression of AD in patients. However, Zaman hypothesized that the constant increase in intracellular calcium during neuronal stimulation may burden hippocampal neurons, causing them to die or improperly function. The neuronal architecture may be altered to compensate for the changes associated with mutant PS1 expression. Zaman proposed that pharmacologic agents aimed at decreasing the synaptic activity, such as benzodiazapines, may thus be protective in AD. This concept is also supported by the pre-filing Fastbom reference, in which a clinical study showed a decrease in the incidence of AD chronic users of benzodiazepines.

Furthermore, the art also teaches that blockade of synaptic potentiation may be beneficial for the prevention of neuronal damage. Fastbom *et al.* teach that GABA receptor activation protects against neural damage due to ischemia and Alzheimer's. According to Muir *et al.* (cited in the IDS filed February 16, 2001), $GABA_A$ agonists may reduce or increase glutamate-induced excitotoxicity *in vitro*, depending on the energy state of the neuronal cell. GABA receptor activation has been studied as a means for reducing brain damage in animal models of ischemia. Muir teaches that $GABA_A$ receptor activation has a deleterious effect on energy-depleted neurons. As Muir stated on page 1217, last paragraph: "Strategies aimed at eliminating [neuronal damage] – for example, the addition of NMDA receptor blockade-might further enhance the neuroprotective effect of $GABA_A$ agonists in the ischemic brain." Zaman *et al.* also demonstrate the operability of the invention on page 57, column 1, lines 9-20: "Blockade of

inhibition with the $GABA_A$ receptor antagonist picrotoxin is known to increase LTP in wild-type animals (Wigstrom & Gustafsson, 1986) by allowing more depolarization and greater activation of NMDA receptors, resulting in a higher rise in intracellular calcium concentration. In picrotoxin, potentiation was increased only in wild-type animals. Under these conditions, we found no significant differences between WT(NT) and mutants (Fig 2b). Thus, it appears that the effect of the ΔE9 mutation on potentiation is occluded by blockade of inhibition."

The present methods for screening for drugs for the treatment of Alzheimer's disease also show that reduction in the enhanced synaptic potentiation of the mutant hippocampal cells is indicative of the activity of a candidate drug. Thus, based on the knowledge present at the time this application was filed, as described above, and with the operability of the present methods confirmed by Zaman *et al*, the skilled artisan would recognize the operability of the present invention with regard to the "correlation of reduced synaptic potentiation with improved memory and learning" (as stated by the Examiner), in that drugs known to worsen memory, such as benzodiazepines (pre-filing Evans *et al.* cited in the IDS filed February 16, 2001, stated that benzodiazepines are known to worsen memory), may be beneficial in treating Alzheimer's disease, providing time and dosing of the drugs are carefully considered. Pre-filing Fastbom *et al.* demonstrated that the time and dosing of this drug is essential to lower the incidence of Alzheimer's disease. Obviously, levels that lead to protection rather than excitotoxic effects are desirable, and a range of concentrations that may be effective could be tested with a screening method such as that provided by the present invention.

> **The in vivo model's (sic) referred to by applicants have not been evaluated as to context as the references have not been provided to the examiner. However, the appendix summaries do not appear to support the correlation of reduced synaptic potentiation with improved learning and memory as desired in Alzheimer's patients and treatments. It is noted that the references appear to be post-filing date evidence which is insufficient to provide a nexus for enablement at the time of invention.**

Applicants believe that this aspect of the rejection appears more similar to a utility rejection than an enablement rejection, since the Examiner's statement "do not appear to support the correlation of reduced synaptic potentiation with improved learning and memory as desired in Alzheimer's patients and treatments" appears to be directed in that regard. As applicants noted

in their response filed February 16, 2001, the claimed screening method is directed to screening for drugs, not determination of dosages. The use of drug screening methods is widespread in the art and, indeed, drug discovery rarely takes place without one or more screening methods in the R&D pathway. ***If*** the present invention were directed to therapeutics, then *in vitro* evidence pertaining to efficacy would be sufficient to establish utility, to which this part of the rejection seems to be addressed (*Cross v. Iizuka*, 753 F.2d 1040 Fed. Cir. 1985). Furthermore, there is no need to provide an *in vivo* model for a ***screening method*** since the functions of screening methods and *in vivo* models are distinct; the former reduces a pool of potentially-useful pharmacological agents, at lower cost and higher-throughput, without need to take into account numerous variables that may occur *in vivo*. There are a number of diseases that occur in humans but lack an animal model that properly mimics the human condition (e.g., gonorrhea, cholera), but this does not preclude efforts to find treatments with *in vitro* methods, particularly using various screening methods. Applicants have provided examples of *in vivo* models of Alzheimer's disease only because the Examiner has previously stated that such models do not exist, and not to correlate the present invention with "improved learning and memory", which is not directly related to the present invention, and not claimed. Accordingly, the Examiner is respectfully requested to withdraw the rejection.

35 U.S.C. 112, second paragraph

> **Claims 6 and 8-9 are rejected under 35 U.S.C. 112, second paragraph, as set forth in Paper No. 3 mailed 10-12-00 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "significant change" in said claims is a relative term which renders the claims indefinite. The specification does not provide a standard for ascertaining the requisite degree of change required to exactly constitute "significant change", and one skilled in the art would not be reasonably apprised of the scope of the invention.**

Applicants respectfully dispute the Examiner's assertion that " 'significant change' is indefinite", both in general, and in the manner supported by the present specification, since there is reference and guidance as to what the significant change to which the claims refer is.

Merriam-Webster's Collegiate Dictionary, 2001 ed., defines "significance" as:

1 a : something that is conveyed as a meaning often obscurely or indirectly

b : the quality of conveying or implying

2 a : the quality of being important

b : ***the quality of being statistically significant*** (emphasis added)

"Statistical significance" is art-recognized as the probability of rejecting a null hypothesis in a statistical test when it is true (Merriam-Webster's Collegiate Dictionary also provides this definition).

It is well known in the art that a t-test may be used to determine significance. It is also generally recognized in the art that a 5% level of significance is acceptable for rejecting a null hypothesis. Statistical significance following a t-test evaluation is often expressed as "$p< 0.05$", an art-recognized level.

Applicants also point out once again that each and every experiment in the present application provides statistical significance for the data presented. One may find the level of t-test significance for Figure 1 on page 4, line 9; for Figure 2 on page 4, line 28; for Figure 3 on page 5, line 28; and for Figure 4 on page 6, line 23. Furthermore, data provided with values ± standard error of the mean may be used to represent and determine the level of significance of the data (page 4, lines 17-26). Applicants respectfully point out that the statistical significance provided by the descriptions of the relevant figures and the associated data in the specification provides support for the claims, since each and every example provides statistical significance for the data.

Applicants once again point out that there is no specific requirement to describe the level of statistical significance in the claims. In fact, claims in U.S. patents generally do not include levels of significance in spite of the myriad use of phrases such as "greater than", "less than", "significant change" and the like. Applicants have found 73 patents issued between 1996 and 2001 with the phrase "significant change" with no actual measure of significance provided in the claims. The number of patents with the phrase "greater than" in the claims with no actual measure of statistical significance appears to be far higher. However, Applicants respectfully note that this is not the intended meaning of the phrase "significant change" but rather the ordinary meaning of an important change as compared to the control.

Accordingly, the Examiner is respectfully asked to withdraw the rejection.

Information Disclosure Statement:

The information disclosure statement filed 2-16-01 fails t comply with 37 CFR 1.98(a)(2) which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Applicants have attached copies of each publication listed in the information disclosure statement filed February 16, 2001.

35 U.S.C. 101, Double Patenting

Claims 1 and 3-13 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 09/193,221 (sic).

Once again, and as noted in the response filed February 12, 2001, the rejection is avoided since the parent ***application*** 09/193,221 is now abandoned in favor of the instant application, and the issue is thus moot. Accordingly, the Examiner is respectfully asked to withdraw the rejection.

35 U.S.C. 112, first paragraph

Claims 10-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims recite "with a candidate drug that is not an antibody", which recitation constitutes new matter. The specification does not support the specific exclusion as claimed. Antibodies may be drugs and used as such. Applicants should point to the specification where support may be found for the exclusion of antibodies as drugs.

This rejection is respectfully traversed. Applicants note that an exact match of the language in the specification and the claims is not required. Support for the use of the phrase "a candidate drug that is not an antibody" is provided by the numerous examples of drugs that are cited in the specification and that are not antibodies, including on page 4, lines 11-12 (agents which affect the $GABA_A$ receptor; line 29 (picrotoxin); page 5, line 12 (flunitrazepam); page 6, line 8 (NBQX); and on page 28 (AP5), none of which are antibodies. Accordingly, the Examiner is respectfully asked to withdraw the rejection.

Claims 1 and 3-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed inventi n. The claims recite "contacting mutant hippocampal cells, with a presenilin gene mutation." It is unclear to the artisan how the cell is contacted with a gene mutation. It appears applicant may be intending to recite a cell having a presenilin gene mutation. Applicants should particularly note the elements of the claims which are intended to be contacted.

This rejection is avoided by the amendment of independent Claims 1, 5, 6, and 8-10, which are now directed to "contacting hippocampal cells comprising a ..." to avoid any syntactic confusion. Accordingly, the Examiner is respectfully asked to withdraw the rejection.

Claims 1 and 3-13 are rejected under 35 U.S.C., first paragraph, as containing subject matter which was not described in the specification in such a was as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection. The claims recite a "presenilin gene mutation," however, no "gene " is described.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*. (See page 1117). However, the specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed," (see Vax-Cat at page 1116) because as set forth in Lewin, Ed., Genes IV, Oxford Univ. Press, 1990, p. 810, a gene is the segment of DNA involve in producing a polypeptide chain and includes regions preceding and following the coding region as well as the intervening sequences. In contrast, applicants specification merely discloses cells having the PS-1 Δ9 mutation (recognized by the artisan as disclosed in the example of Crook et al., Nature Medicine 1998 April 4(4):452-5). Thus, the encompassed sequences of the PS-1 Δ9 mutation appear to be described, however that encompassed by a presenilin gene is not, for example including upstream and downstream sequences of the "gene" which direct expression in the organism. Thus, the specification does not disclose the "gene" as claimed or enable the artisan recognition of the encompassed mutations. With the exception of the PS-1 Δ9 mutation, the skilled artisan cannot envision the detailed structure of the encompassed components and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel USPQ 2d 1601 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Lts., 18 USPQ2d 1016.

This rejection is respectfully traversed for the following reasons.

First, regarding Amgen Inc. V. Chugai Pharmaceutical, the court held that conception of a DNA invention "has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated." *Id.* at 1206. The *Fiers* court held that "[i]f a conception of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical

properties, as we have held, then a description also requires that degree of specificity".

Applicants respectfully point out that, with regard to the present invention, these court cases are not relevant because what is being claimed is not an ***isolated gene*** or ***a DNA***. Considering Claims 1 3-5, 7-9 and 13 as a whole, what is covered is "a method for screening drugs for the treatment of Alzheimer's disease." Claim 6 is directed to a method for determining whether a mutation in hippocampal cells acts on a common pathway with a $GABA_A$ receptor antagonist. Claims 10-12 are directed to slices of mouse hippocampal tissue containing cells comprising a mutation combined with a candidate drug. The present invention does not claim an ***isolated gene*** or ***a DNA*** as a genus, rather the claimed invention falls within a field that is a well-known and predictable art (i.e., electrophysiology). Furthermore, the specification contains numerous examples, descriptions and drawings that provides representative species for the present invention by studying the effects of a variety of drugs using several direct and comparative methods. The specification does indeed "enable the artisan recognition of the encompassed mutations " since all of the cells with mutations must have enhanced synaptic potentiation upon stimulation as compared to wild-type cells and slices of mouse hippocampal tissue and subjecting the cells to a tetanic stimulus, said phrase in itself being sufficient "to define the invention by functional characteristics coupled with a known or disclosed correlation" (see USPTO docket no. 980605148-8148-01 *Request for Comments on Interim Guidelines for Examination of Patent Applications under 35 USC 11 para. 1 "written description"*), and *Revised Interim Written Description Guidelines Training Materials/ Synopsis of Application of Written Description Guidelines,* page 8). In this instance, the skilled artisan would know that the functional definition of "enhanced synaptic potentiation upon stimulation as compared to wild-type cells" imparts "reasonable clarity" (see *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111) would be sufficient to understand the present invention, and that Applicants were in possession of the invention at the time the application was filed.

Second, the filing of an application is a constructive reduction to practice providing the specification is enabling. Throughout the specification, applicants have taught how to make and use the present invention, and have exemplified the invention with several examples. The written description requirement for a claimed genus may be satisfied through sufficient description of a

representative number of species by relevant identifying characteristics., i.e., structure or other physical characteristics, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that the applicant was in possession of the claimed genus (see PTO Request for Comments, *supra*).

Accordingly, the Examiner is respectfully requested to withdraw the rejection.

CONCLUSION

In view of the above remarks, it is submitted that this application is now ready for allowance. Early notice to that effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 328-4400.

Respectfully submitted,

Dated: November 9, 2001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Malinow *et al.*	Examiner: S. L. Turner
Serial No.: 09/353,126	Art Unit: 1647
Filed: July 14, 1999	
For: Diagnostic methods for drug screening for Alzheimer's disease	**VERSION OF AMENDED CLAIMS WITH MARKINGS TO SHOW CHANGES MADE**

BOX AF
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

These marked-up versions of the amended claims accompany the attached Response to Office Action of May 9, 2001 for the above identified patent application.

IN THE CLAIMS:

1. (Amended) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting [mutant] hippocampal cells[, with] comprising a presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells to tetanic stimulation; and

determining the effect of said candidate drug on the synaptic potentiation of said mutant hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

CERTIFICATE OF FIRST CLASS MAILING

I hereby certify that this paper or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Assistant Commissioner For Patents, Washington, D.C.20231

on Date: November 9, 2001

Signature: [signature]

Printed Name: Jeffrey M. Libby

5. (Amended) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting [mutant] hippocampal cells[, with] comprising a presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to a tetanic stimulus;

measuring changes in potentiation with time of the mutant hippocampal cells and wild-type hippocampal cells and comparing the effect of said candidate drug on the synaptic potentiation of said mutant hippocampal cells as compared to the observed synaptic potentiation of said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells as compared to the synaptic potentiation of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

6. (Amended) A method for determining whether a mutation in hippocampal cells acts on a common pathway with a $GABA_A$ receptor antagonist, said method comprising:

contacting [mutant] hippocampal cells[, with] comprising a presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a $GABA_A$ receptor antagonist;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to tetanic stimulation; and

measuring changes in synaptic potentiation with time of said mutant hippocampal cells and said wild-type hippocampal cells and comparing the effect of said $GABA_A$ receptor antagonist on said mutant hippocampal cells and said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells without a significant change in the synaptic potentiation of the wild-type cells is indicative of the mutation acting on a common pathway with said $GABA_A$ receptor antagonist.

8. (Amended) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting [mutant] hippocampal cells[, with] comprising a presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to a tetanic stimulus at a first potential of glutamate currents and a second potential of $GABA_A$ currents;

measuring the synaptic response at each of the first and second potentials for said mutant hippocampal cells and said wild-type hippocampal cells and comparing the effect of said candidate drug on said mutant hippocampal cells and said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic response of the mutant hippocampal cells without a significant change in the synaptic response of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

9. (Amended) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting [mutant] mouse hippocampal cells [mutated in the] comprising a presenilin-1 gene mutation and having enhanced synaptic potentiation upon tetanic stimulation as compared to wild-type hippocampal cells, with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to tetanic stimulation; and

comparing the effect of said candidate drug on said mutant hippocampal cells and said wild-type hippocampal cells upon tetanic stimulation;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells without a significant change in the synaptic potentiation of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

Add Claims 14-26.

--14. (New) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting hippocampal cells comprising a PS-1 Δ9 presenilin gene mutation wherein said hippocampal cells have enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells to tetanic stimulation; and

determining the effect of said candidate drug on the synaptic potentiation of said mutant hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

15. (New) The method according to Claim 14, wherein mouse hippocampal tissue slices comprise said mutant hippocampal cells.

16. (New) The method according to Claim 14, wherein said enhanced synaptic potentiation is a result of a change in the $GABA_A$ receptor pathway.

17. (New) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting hippocampal cells comprising a PS-1 Δ9 presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to a tetanic stimulus;

measuring changes in potentiation with time of the mutant hippocampal cells and wild-type hippocampal cells and comparing the effect of said candidate drug on the synaptic potentiation of said mutant hippocampal cells as compared to the observed synaptic potentiation of said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells as compared to the synaptic potentiation of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

18. (New) A method for determining whether a mutation in hippocampal cells acts on a common pathway with a $GABA_A$ receptor antagonist, said method comprising:

contacting hippocampal cells comprising a PS-1 Δ9 presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a $GABA_A$ receptor antagonist;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to tetanic stimulation; and

measuring changes in synaptic potentiation with time of said mutant hippocampal cells and said wild-type hippocampal cells and comparing the effect of said $GABA_A$ receptor antagonist on said mutant hippocampal cells and said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells without a significant change in the synaptic potentiation of the wild-type cells is indicative of the mutation acting on a common pathway with said $GABA_A$ receptor antagonist.

19. (New) The method according to Claim 18, wherein said candidate drug is present with said wild-type hippocampal cells.

20. (New) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting hippocampal cells comprising a PS-1 Δ9 presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to a tetanic stimulus at a first potential of glutamate currents and a second potential of $GABA_A$ currents;

measuring the synaptic response at each of the first and second potentials for said mutant hippocampal cells and said wild-type hippocampal cells and comparing the effect of said candidate drug on said mutant hippocampal cells and said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic response of the mutant hippocampal cells without a significant change in the synaptic response of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

21. (New) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting mouse hippocampal cells comprising a PS-1 Δ9 presenilin-1 gene mutation and having enhanced synaptic potentiation upon tetanic stimulation as compared to wild-type hippocampal cells, with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to tetanic stimulation; and

comparing the effect of said candidate drug on said mutant hippocampal cells and said wild-type hippocampal cells upon tetanic stimulation;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells without a significant change in the synaptic potentiation of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

22. (New) Slices of mouse hippocampal tissue containing cells having a mutation in a presenilin gene combined with a candidate drug that suppresses intracellular calcium rise in said cells.

23. (New) Slices of mouse hippocampal tissue containing cells according to Claim 22, after tetanic stimulation.

24. (New) Slices of mouse hippocampal tissue containing cells having a PS-1 Δ9 mutation in a presenilin gene combined with a candidate drug that suppresses intracellular calcium rise in said cells.

25. (New) Slices of mouse hippocampal tissue containing cells according to Claim 24, after tetanic stimulation.

26. (New) A method for screening for a candidate drug that suppresses intracellular calcium rise in slices of mouse hippocampal tissue containing cells having a PS-1 Δ9 mutation in a presenilin gene combined with a candidate drug for the treatment of Alzheimer's disease, said method comprising:

contacting hippocampal cells comprising a presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug that suppresses intracellular calcium rise in said cells;

subjecting said mutant hippocampal cells to tetanic stimulation; and

determining the effect of said candidate drug on the ratio of peak inhibitory to excitory responses;

wherein an enhanced said ratio of peak inhibitory to excitory responses in said mutant hippocampal cells as compared to wild-type hippocampal cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.--

CONCLUSION

Should the Examiner have any questions regarding the above, the Examiner is invited to call the undersigned.

Respectfully submitted,

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